REMARKS

Status of the Claims

Claims 1-14 are pending as shown above.

Priority

The specification was objected to for not including the priority claim to U.S. Patent Application No. 10/912,932. (Office Action, pages 2-3).

Applicants have amended the specification to specify that the instant application is a continuation of U.S. Patent Application No. 10/912,932, thereby obviating the rejection.

Information Disclosure Statement

Applicants acknowledge receipt of the signed and initialed PTO forms indicating the Information Disclosure Statements submitted April 25, 2007 and April 22, 2008 have been considered.

Specification

The Abstract was objected to because it was not a single paragraph. (Office Action, page 4). In addition, the disclosure was objected to for containing an embedded hyperlink. *Id.* Finally, the use of trademarks were noted and it was indicated they should be capitalized wherever they appear. (Office Action, pages 4-5).

Applicants have amended the Abstract and Specification as shown above, thereby obviating the objections.

Double Patenting

Claims 1-9 were provisionally rejected under the judicially-created doctrine of non-obviousness type double patenting over copending Application No. 11/304,981 in view of U.S. Patent No. 5,916,794 as well as over copending Application Nos. 10/912,932 and 12/456,857. ((Office Action, pages 6-10).

Applicants request that the provisional rejections be held in abeyance until patentable subject matter is found in this or the other applications.

35 U.S.C. § 103(a)

Claims 1-14 were rejected under 35 U.S.C. § 103(a) as allegedly obvious over U.S. Patent No. 5,916,795 (hereinafter "Chandrasegaran") in view of Smith et al. (2000) *Nucleic Acids Res.* 28:3361-3369 (hereinafter "Smith"). (Office Action, pages 11-14). Chandrasegaran was cited for teaching all the elements of the claims except the recitation that the zinc finger DNA-binding domains are engineered to bind to target sequence located between 2 and 50 nucleotides apart, which was alleged to be taught by Smith. *Id.*

Applicants traverse the rejection and supporting remarks.

There is no combination of Chandrasegaran and Smith that teaches the recited elements of the claims methods. It is axiomatic that in order to establish a prima facie case of obviousness, the cited references must teach all the elements of the claims. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Moreover, an obviousness rejection can only be sustained when the proposed combination of elements results in a predictable outcome. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398; 82 USPQ2d 1385, 1397 (2007).

As acknowledged, Smith is entirely silent as to methods of cleaving cellular chromatin using fusion proteins as claimed. Thus, in order establish a *prima facie* case of obviousness, Chandrasegaran must teach not only fusion proteins in which the cleavage domain is closer to the C-terminus of the fusion protein and the zinc finger protein is closer to the N-terminus of the protein, this reference must also teach that fusion proteins with the claimed orientation predictably cleave cellular chromatin. Chandrasegaran fails to teach the claimed methods and, accordingly, the rejection cannot be sustained.

Chandrasegaran does not teach that fusion proteins in which the cleavage domain is closer to the C-terminus of the fusion and the zinc finger protein is closer to the N-terminus are functional. While col. 18, lines 28-31 are cited as disclosing it is "possible" to construct such fusion proteins, the reference does not in any way teach that the claimed configuration is functional. In fact, Chandrasegaran teaches only constructs having the opposite configuration to that claimed, namely constructs in which the cleavage domain is closer to the N-terminus and the zinc finger protein is closer to the C-terminus (col. 7, lines 4-7):

> This construct links the zinc finger proteins through the glycine linker to the C-terminal 196-amino acids of FokI that constitute the FokI cleavage domain (8). This construct also tags the hybrid protein with six consecutive histidine residues at the N-terminus.

Furthermore, Chandrasegaran indicates that the constructs disclosed were made by replacing the Ubx homeodomain of Kim et al. (1994)'s fusion of Ubx-FokI (ref. 8 in Chandrasegaran, Ref. C46 of IDS submitted April 25, 2007) with the zinc finger domains (col. 6, lines 33-35):

> This construct replaces the Ubx homeodomain with the genes encoding the zinc finger proteins.

As clearly set forth in Kim (and therefore Chandrasegaran), the FokI domain is linked to the C-terminal of Ubx. *See, e.g.,* Figure 1 of Kim showing the orientation of Ubx-FokI fusion and showing that the FokI domain is fused to the C-terminal of Ubx:

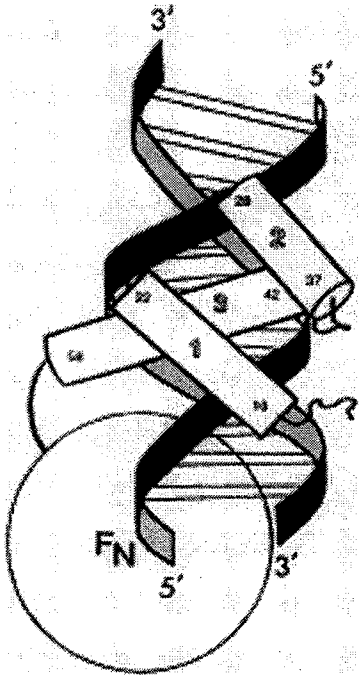
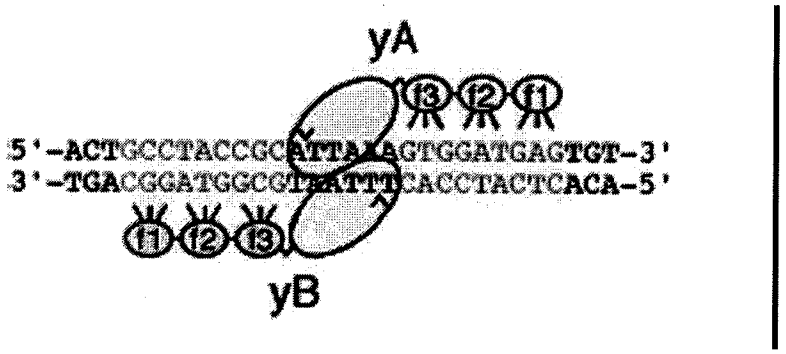


FIG. 1. Diagram showing orientation of the Ubx homeodomain with respect to the *Fok* I nuclease domain (F_N) in relation to the DNA substrate. The crystal structure of an Engrailed homeodomain–DNA complex was reported by Kissinger *et al.* (16).

Hence, the only configuration disclosed in Chandrasegaran that is shown to be functional is one in which the FokI domain is linked to the C-terminal of the zinc finger protein. This is entirely unlike the claimed methods.

Still further evidence that fusion protein configurations as claimed are not taught by Chandrasegaran is found in Bibikova et al. (2002) (Ref. C7 of IDS submitted April 25, 2007). Indeed, Bibikova evidences that it was not known to the skilled artisan at the time of filing that the cleavage domain could be linked to the N-terminus of the zinc finger protein. As described in Bibikova, the only configuration known to the skilled artisan at the time of filing for zinc finger nucleases was one in which the cleavage domain was linked to the C-terminus of the zinc finger protein. See, Figure 1 of Bibikova showing the cleavage domain of yA and yB ZFNs linked to the C-terminus (finger 3 shown as "f3") of the zinc finger protein:



Thus, Bibikova establishes that prior to the instant application (and well after Chandrasegaran), zinc finger protein-FokI fusions were only made by fusing the FokI domain to the C-terminus of the zinc finger protein.

As Chandrasegaran does not teach recited elements of the pending claims, *i.e.,* functional fusion proteins in the specifically claimed orientation of zinc finger domain relative to cleavage domain, the rejection cannot stand.

The obviousness rejection is improper because the claimed methods (in which the orientation of at least one zinc finger-cleavage domain fusion is as recited) was not predictable from the opposite orientation taught in the art. The Examiner has not pointed, and indeed cannot point, to any evidence that shows the claimed configuration of fusion protein would be functional in cleaving cellular chromatin.

Furthermore, the claimed fusion proteins provide unexpected and surprising results as compared to previously-known fusion proteins. As detailed in Example 27 of the as-filed specification (and shown in Figures 44 and 45), the polarity of the individual zinc finger nucleases can significantly affect cleavage efficacy. For instance, when both target sites are on the same strand, only the combination of the nuclease having different polarities from each other was successful in cleaving the substrate (see, Figure 45).

For at least these reasons, withdrawal of the rejection is in order.

CONCLUSION

It is believed the claims are in condition for allowance. If the Examiner notes any further matters that the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact the undersigned.

Respectfully submitted,

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By: _____

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